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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,843	09/17/2001	Sheena M. Loosmore		5498

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EXAMINER	
HINES, JANA A	
ART UNIT	PAPER NUMBER
1645	6

DATE MAILED: 03/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/857,843	LOOSMORE ET AL.	
	Examiner	Art Unit	
	Ja-Na A Hines	1645	

-- The MAILING DATE of this communicati n appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 0199* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. The preliminary amendment filed June 11, 2001 has been entered. Claims 1-24 are under consideration in this office action.

Priority

2. An application in which the benefits of an earlier application, 09/210,995, are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application, 09/210,995 should therefore be included in the first sentence.

Specification

3. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

4. The attempt to incorporate subject matter into this application by reference to 09/167,568 at page 3 line 7; 08/258,228; 08/261,194; 08/483,856 page 6 lines 3-10 and

the like as recited throughout the instant specification is improper because a mere reference to another application, is not an incorporation since the documents do not appear to published. However, if the applications have been published, then the patent number needs to entered in place of the serial number.

5. The disclosure is objected to because of the following informalities: page 6 lines 3 recites "USAN 08/258,228". Appropriate correction is required.

6. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b) therefore, the abstract from the international application will be used in the instant application.

6. The use of the trademarks QS21™, QUIL A™ and other adjuvants listed within the specification have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for immunogenic composition comprising the analog H91A Hin47 having decreased protease activity and a recombinant high molecular weight (rHMW) protein to confer protection against *Haemophilus influenzae*, does not reasonably provide enablement for an immunogenic composition comprising at least two different antigens of *Haemophilus influenzae* where at least one is an adhesin and the other is not an adhesin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification teaches that the specific the construction of an immunogenic composition comprising the analog H91A Hin47 having decreased protease activity and a recombinant HMW protein to confer protection against *Haemophilus influenzae*. See the specification from page 16 and examples 3-7 which describes the combination of H91A Hin47 and rHMW as a two component vaccine. There are no examples within the specification of any other analogs and HMW proteins capable of conferring protection in a host against disease caused by *Haemophilus influenzae*. The specification fails to teach examples of any other combinations that meet the limitations of the claims. The

specification appears to make the conclusion that any immunogenic composition comprising at least two different antigens of *Haemophilus influenzae* wherein at least one is an adhesin and the other is not an adhesin is capable of conferring protection in a host against disease caused by *Haemophilus influenzae* can be used without any substantiating evidence. Therefore, the claims are only enabled for immunogenic composition comprising the analog H91A Hin47 having decreased protease activity and a recombinant HMW protein to confer protection against *Haemophilus influenzae*.

Applicants have provided no guidance as to the nature and extent of the changes that must be made to enable one of ordinary skill in the art how to make, without undue experimentation, an immunogenic composition comprising at least two different antigens of *Haemophilus influenzae* wherein at least one is an adhesin and the other is not an adhesin. Given the lack of guidance contained in the specification and the unpredictability for making an immunogenic composition comprising at least two different antigens of *Haemophilus influenzae* wherein at least one is an adhesin and the other is not an adhesin, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Furthermore, the specification fails to provide an enabling disclosure for the use of any immunogenic composition comprising at least two different antigens of *Haemophilus influenzae* wherein at least one is an adhesin and the other is not an adhesin that meets the limitations recited in the claims. Applicants' have provided no guidance to enable one of ordinary skill in the art as to how determine, without undue experimentation, other immunogenic compositions. There is no requirement for the use

of only the incorporation an H91A Hin47 analog having decreased protease activity and a recombinant HMW protein to confer protection against *Haemophilus influenzae*. Given the lack of guidance contained in the specification and the unpredictability for determining an acceptable immunogenic composition, one skilled in the art could not make or use the broadly claimed invention without undue experimentation.

8. Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 26 provides for the use of at least two different antigens of Haemophilus influenzae in the manufacture of a vaccine, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

9. Claim 26 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-22 and 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barenkamp et al., (WO 97/36,914) in view of Loosmore et al. (US Patent 5,506,139). Barenkamp et al., (WO 97/36,914), teach high molecular weight (HMW) surface proteins of non-typeable Haemophilus. The high molecular weight surface proteins of non-typeable *Haemophilus influenzae* that exhibit immunogenic properties and genes encoding for immunodominant high molecular weight proteins, HMW1, HMW2, HMW3 and HMW4. HMW3 and HMW4 show considerable homology to HMW1 and HMW2 thus HMW3 and HMW4 are also likely to function as adhesins (page 18 lines 14-17). These HMW proteins are related to filamentous hemagglutinin surface proteins, wherein these proteins cause an increased antibody response (page 5 lines 30-35). The immune response to these proteins may be either humoral or a cell-mediated (page 7 lines 18-25). The invention teaches an immunogenic composition comprising the novel high molecular weight protein or synthetic peptides along with a pharmaceutically acceptable carrier for in vivo administration to a host (page 6 lines 20-27). The immunogenic composition may comprise at least one other immunogenic or immunostimulating material and at least one adjuvant (page 7 lines 1-5). Barenkamp et al., (WO 97/36,914), teach a long list of suitable adjuvants including

aluminum phosphate and aluminum hydroxide (page 7 lines 6-17). The high molecular weight proteins can be produced recombinantly (page 10 lines 21-25) and the HMW1 and HMW2 have an apparent molecular weight of 125 and 120 kDa respectively when produced from non-typeable *Haemophilus* (page 15 lines 21-24); while HMW3 and HMW4 have apparent molecular weights of 125 and 123 kDa from non-typeable *Haemophilus*. One example illustrates the use of HMW antigens composed in an immunogenic composition containing 40ug of HMW protein and Freund's adjuvant, the mixture was administered to a host (chinchillas) infected with *Haemophilus influenzae* causing otitis media (pages 47-48 lines 29-33). Barenkamp et al., (WO 97/36,914), teach complexing additional components to the antigenic composition to enhance immune response including herpes simplex virus vaccine, pseudorabies virus vaccine, tetanus toxoid, poliomyelitis virus vaccine, hepatitis B virus antigen and others (page 24-25 lines 7-10). Finally, Barenkamp et al, (WO 97/36,914), data teach that the adhesin proteins are potentially important protective antigens which should comprise one component of a multi-component non-typeable *H. influenzae* vaccine (page 49 lines 15-19). Barenkamp et al., (WO 97/36,914), however do not teach the combination of different antigens of *H.influenzae* wherein the other antigen is a heat shock protein in an immunogenic composition.

Loosmore et al., teach analogs of *Haemophilus* Hin47 with reduced protease activity. The Hin47 heat shock protein is immunologically conserved among strains of *Haemophilus influenzae* and is reported to have utility in vaccination against disease caused by *H. influenzae* or other bacterial pathogens that produce Hin47 or proteins

capable of raising antibodies specifically reactive with Hin47 (col. 2 lines 16-21). The Hin47 protein is a protein that is an outer membrane protein with a molecular weight of about 47Kd (col. 2 lines 4-6). Therefore, Loosmore et al., teach that it would be advantageous to provide analogs of Hin47 that are substantially reduced in proteolytic activity for use as an antigen or to be included in other immunogenic preparations (col. 2 lines 29-34). The isolated and purified analog of *Haemophilus influenzae* has decreased protease activity which is less than about 10% of natural Hin47, yet still retains substantially the same immunogenic properties, where at least one amino acid contributing to protease activity may be deleted or replaced by a different amino acid to produce reduced activity (col. 2 lines 44-54). "The at least one deleted or replaced amino acid may be selected from amino acids 195-201 of Hin47, and specifically may be Serine-197, which may be deleted or replaced by alanine. In addition, the at least one deleted or replaced amino acid may be Histidine-91 and may be deleted or replaced by alanine or lysine or arginine. Furthermore, the at least one deleted or replaced amino acid may be Asparagine-121 and may be deleted or replaced by alanine or glutamic acid" (col. 2 lines 56-64). An immunogenic composition comprising an immuno-effective amount of Hin47 analog may be formulated as a vaccine for *in vivo* administration to a host; including a human to confer protection against diseases caused by a bacterial pathogen, such as *Haemophilus influenzae* (col. 3 lines 47-59). The immunogenic composition may further comprise at least one other immunogenic or immunostimulating material such as an adjuvant, and may be contained within a live vector such as a pox-virus, salmonella, poliovirus, adenovirus, vaccinia or BCG (col. 3-4

lines 60-2). Additional embodiments allow for the incorporation of glyoconjugates to confer protection against disease and infection caused by any bacteria having polysaccharide antigens, such as lipopolysaccharides and polyribosyl ribotol phosphate (PRP) toxin wherein pathogens may include *Streptococcus pneumoniase, E. coli, Neisseria meningitides, Salmonella typhi* and a variety of others (col. 7 lines 37-51). The analogs may be used as carrier proteins to make conjugate vaccines against antigenic determinants unrelated to Hin47 including pathogenic bacteria (col. 7 lines 15-18 and 40-51). The Hin47 vaccines elicit an immune response that produces antibodies including anti-Hin47 antibodies, and opsonizing or bactericidal antibodies (col. 8 lines 20-31). The Hin47 analogs may be prepared with pharmaceutically acceptable carriers or adjuvants such as aluminum hydroxide or phosphate and should be administered in dosage ranges readily determinable by one skilled in the art (col. 8-9 lines 33-6). Vaccines can be combined with material from various or the same pathogen or from various strains of the same pathogen or from combinations of various pathogens (col. 9 lines 14-20). Combined vaccines which contain antigenic material from various pathogens are also taught (col. 9 lines 15-20). Example 10 illustrates the comparative immunogenicity of a Hin47 analog in mice, while example 11 illustrates the immunoprotective properties of the Hin47 analog. Table 2 shows the protective ability of anti-Hin47 mutant antiserum against *H.influenzae* infant rat model of bacteremia.

One would expect a reasonable level of success by combining the well known HMW adhesin proteins and the well known Hin47 analogs in a multi-component immunogenic composition since both Barenkamp et al., (WO 97/36,914), and Loosmore et al., teach the use the these antigens in immunogenic compositions against *Haemophilus influenzae*. Furthermore, both Barenkamp et al., (WO 97/36,914) and Loosmore et al., teach the use of adjuvants; the addition of antigenic components; and methods for immunizing a host against disease caused by an infection with *H. influenzae* comprising administration of the immunogenic composition. No more than routine skill was required at the time of appellants invention to combine two well known compositions, i.e., two different antigens of *H.* influenzae, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for that very same purpose of providing an immunogenic composition.

Therefore it would have been obvious at the time of applicant's invention to have an immunogenic composition to confer protection against *Haemophilus influenzae* comprising at least two different antigens, wherein one is a heat shock protein as taught by Loosmore et al., and the other is a high molecular weight adhesin protein, HMW1 or HMW2 which are important protective antigens as taught by Barenkamp et al., (WO 97/36,914), because Loosmore et al., teach that analogs of Hin47 with reduced protease activity from *Haemophilus influenzae* are useful in vaccination against diseases caused by *H. influenzae* or other bacterial pathogens and these proteins are capable of eliciting protective opsonizing or bactericidal antibodies.

11. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barenkamp et al., (WO 97/36,914) and Loosmore et al. (US Patent 5,506,139) in view of Anilionis et al. (US Patent 5,098,997). Barenkamp et al., (WO 97/36,914) and Loosmore et al. (US Patent 5,506,139) have been discussed above, however neither teach an immunogenic composition comprising pertussis antigens.

Anilionis et al., teach outer membrane protein vaccines for *Haemophilus influenzae*. These outer membrane proteins can be used as immunogens in vaccines and coupled to protein carriers such as diptheria toxin, tetanus toxin or pertussis toxin or toxoid (col. 22 lines 40-50). Also taught are formulations for vaccines.

Therefore, no more then routine skill would have been required at the time of applicants invention to use the pertussis antigen as taught by Anilionis et al., in the immunogenic composition using other well known antigens as taught by Barenkamp et al., and Loosmore et al., because it is well known in the art that the petussis toxin is traditionally found in multivalent protective vaccines.

Double Patenting

12. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

13. Claims 6-24 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 6-24 of copending Application No. 09/210,995. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

14. Claims 1-5 and 25-26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-24 of copending Application No. 09/210,995. Although the conflicting claims are not identical, they are not patentably distinct from each other because no more then routine skill would have been required at the time of applicant invention to use the claimed immunogenic composition is: embraced by the composition recited in claims 6-24; and useable in a method of immunizing a host against *Haemophilus influenzae* because the art teaches that it would have been obvious at the time of applicant's invention to use an immunogenic composition comprsing two different *Haemophilus influenzae* antigens to confer protection against *Haemophilus influenzae* since they are known to be protective in vaccinations against diseases caused by *H. influenzae* and these compositions are capable of eliciting protective opsonizing or bactericidal antibodies.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Prior Art

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Barenkamp (64(4): 1246-51) teaches immunization with high-molecular weight adhesion proteins of NTHi. Barenkamp et al., (64(8): 3032-37) teach identification of surface exposed b-cell epitopes on HMW adhesion proteins of NTHi. Krivan et al., (WO 94/00149) teach adhesin-oligosaccharide conjugate vaccine for *H. influenzae*. Loosmore et al., (WO 96/03506) teach analog of Hin47 with reduced protease activity. Loosmore et al., (66(3): 899-906) teach *H. influenzae* HtrA protein is a protective antigen.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na A Hines whose telephone number is 703-305-0487. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 703-308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communication.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ja-Na Hines
March 16, 2002

PATRICIA A. DUFFY
PRIMARY EXAMINER